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## **Takotsubo (Stress) Cardiomyopathy**

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# Takotsubo (Stress) Cardiomyopathy

**TO THE EDITOR:** Templin et al. (Sept. 3 issue)<sup>1</sup> highlight the fact that takotsubo cardiomyopathy is associated with a substantial rate of adverse events. With this in mind, an important aspect that the authors do not discuss is the prevalence of dynamic left ventricular outflow tract obstruction (LVOTO). Dynamic LVOTO is a condition with a recognized association with takotsubo cardiomyopathy and has been reported in 10 to 20% of patients in much smaller studies.<sup>2-4</sup> This association is important because the coexistence of hemodynamically significant LVOTO and acute left ventricular systolic dysfunction poses a major therapeutic challenge, since the accepted management strategy for either condition alone (i.e., negative inotropy and increased afterload for LVOTO or positive inotropy and reduced afterload for acute left ventricular dysfunction) is potentially catastrophic in the other. Thus, it has been speculated that some patients with takotsubo cardiomyopathy and LVOTO may be best treated with early extracorporeal mechanical circulatory support.<sup>5</sup> Do the authors have any data regarding the prevalence of LVOTO and its management? Given the unsurpassed wealth of data they have accrued on takotsubo cardiomyopathy, this would seem to be an excellent opportunity to more accurately characterize a potentially devastating complication.

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No potential conflict of interest relevant to this letter was reported.

1. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015;373:929-38.
2. El Mahmoud R, Mansencal N, Pillière R, et al. Prevalence and characteristics of left ventricular outflow tract obstruction in Tako-Tsubo syndrome. *Am Heart J* 2008;156:543-8.
3. De Backer O, Debonnaire P, Gevaert S, Missault L, Gheeraert P, Muyldermans L. Prevalence, associated factors and management implications of left ventricular outflow tract obstruction in takotsubo cardiomyopathy: a two-year, two-center experience. *BMC Cardiovasc Disord* 2014;14:147.
4. Shah BN, Curzen NP. Dynamic left ventricular outflow tract obstruction and acute heart failure in tako-tsubo cardiomyopathy. *J Am Coll Cardiol* 2011;58:1195-6, author reply 1196.
5. Bonacchi M, Maiani M, Harmelin G, Sani G. Intractable cardiogenic shock in stress cardiomyopathy with left ventricular

outflow tract obstruction: is extra-corporeal life support the best treatment? *Eur J Heart Fail* 2009;11:721-7.

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**TO THE EDITOR:** In their article on clinical observations from the International Takotsubo Registry, Templin et al. report 30-day mortality of 5.9% among patients with takotsubo cardiomyopathy. In addition, 12.2% of patients received catecholamine-based inotropes. These proportions are higher than those recently reported by the Swedish Health Care Registry on Heart Disease (SWEDEHEART) (4.1% and 5.6%, respectively),<sup>1</sup> and we think that the high short-term mortality could be partially explained by the liberal use of inotropes.

To date, no randomized clinical trial has investigated pharmacologic treatment strategies in patients with takotsubo cardiomyopathy. However, a large body of preclinical and clinical evidence implicates catecholamines in the pathophysiology, which supports the argument that inotropes should be contraindicated in patients with takotsubo cardiomyopathy.<sup>2-4</sup> Templin et al. found that the rate of catecholamine treatment was considerably higher among men than among women (21.0% vs. 11.2%), which corresponded to a higher 30-day mortality among men than among women (12.2% vs. 5.2%). Thus, it would therefore be valuable if the authors could indicate whether the use of catecholamines is an independent predictor of death (after appropriate adjustment for cofounders) in their registry.

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No potential conflict of interest relevant to this letter was reported.

1. Redfors B, Vedad R, Angerås O, et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction — a report from the SWEDEHEART registry. *Int J Cardiol* 2015;185:282-9.
2. Redfors B, Ali A, Shao Y, Lundgren J, Gan LM, Omerovic E. Different catecholamines induce different patterns of takotsubo-like cardiac dysfunction in an apparently afterload dependent manner. *Int J Cardiol* 2014;174:330-6.
3. Redfors B, Shao Y, Ali A, Omerovic E. Current hypotheses regarding the pathophysiology behind the takotsubo syndrome. *Int J Cardiol* 2014;177:771-9.

4. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539-48.

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**TO THE EDITOR:** Templin and colleagues report substantial long-term morbidity and mortality among patients with takotsubo cardiomyopathy. In their diagnosis of this condition according to Mayo Clinic criteria, they do not clarify how they ruled out myocarditis. Myocarditis may present with apical ballooning that mimics takotsubo cardiomyopathy.<sup>1</sup> Indeed, the inclusion of patients with atypical forms, particularly the focal type, may have further increased the risk of enrolling patients with myocarditis. Among patients who have left ventricular dysfunction, an increase in troponin levels, and normal coronary arteries, myocarditis cannot be reasonably ruled out without endomyocardial biopsy or cardiac magnetic resonance imaging (MRI).<sup>2</sup> Myocardial edema without delayed enhancement is a typical feature of takotsubo cardiomyopathy,<sup>3</sup> which allows for distinction from myocarditis on MRI.

The possible inclusion of patients with myocarditis in the study could have substantially increased the event rate. Caforio and colleagues reported a 6-year rate of death or heart transplantation of 27% among patients with biopsy-proven myocarditis, with biventricular dysfunction at presentation and the presence of virus on genomic analysis of myocardium being the best predictors of an adverse outcome.<sup>4</sup> Thus, the exclusion of myocarditis is crucial to refining the patient population and assessing the prognosis of patients with takotsubo cardiomyopathy.

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No potential conflict of interest relevant to this letter was reported.

1. Caforio AL, Tona F, Vinci A, et al. Acute biopsy-proven lymphocytic myocarditis mimicking Takotsubo cardiomyopathy. *Eur J Heart Fail* 2009;11:428-31.

2. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;34:2636-48.

3. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance

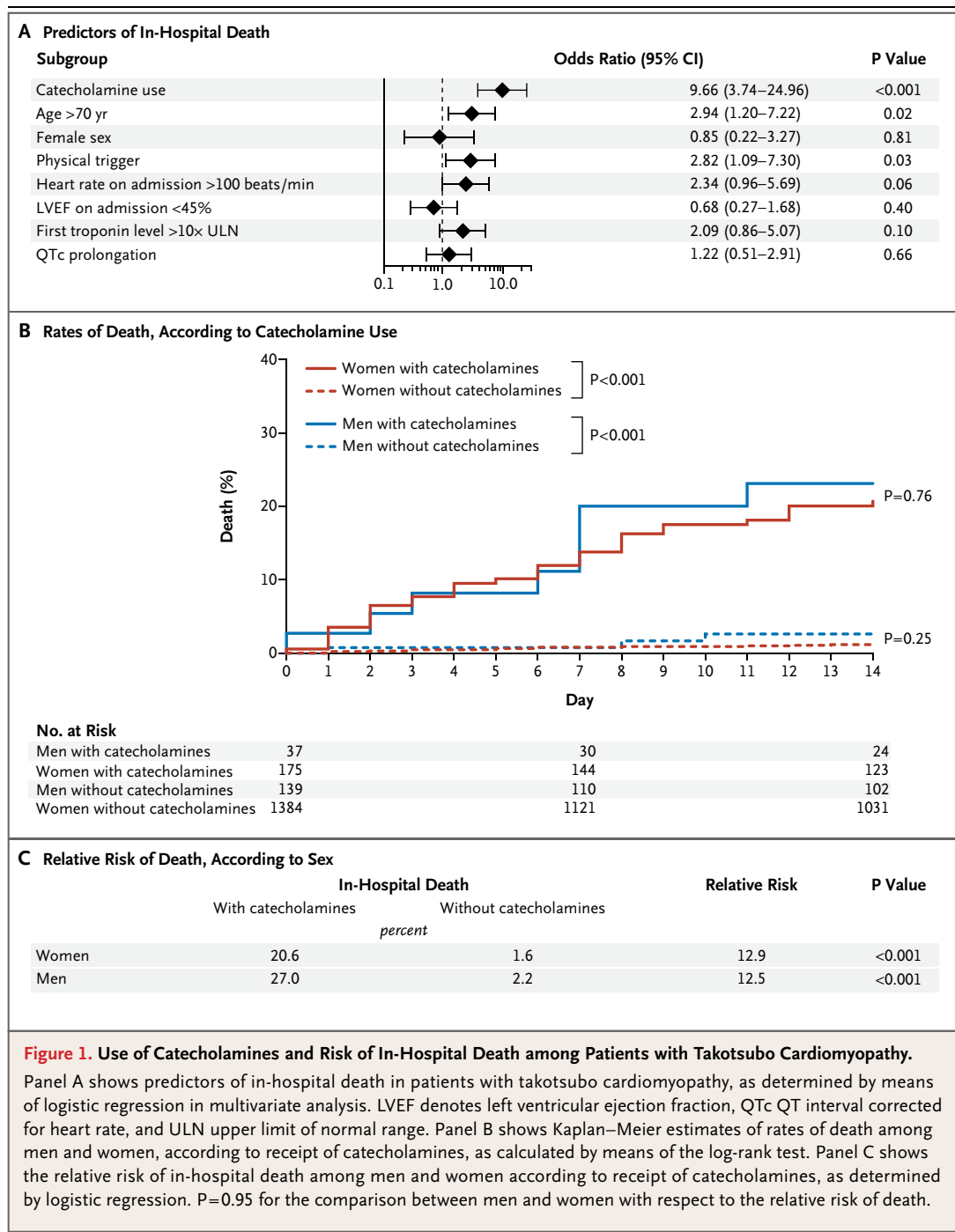
findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011;306:277-86.

4. Caforio AL, Calabrese F, Angelini A, et al. A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. *Eur Heart J* 2007;28:1326-33.

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**THE AUTHORS REPLY:** In response to the comments of Dalzell: LVOTO occurs in approximately 20% of patients with takotsubo cardiomyopathy<sup>1</sup> and may also develop later during the acute phase. It can be precipitated by inotropes and poses a substantial risk to the patient. Therefore, careful evaluation for the presence of a pressure gradient during angiography should be performed, as well as serial echocardiography to systematically rule out the development of LVOTO later during hospitalization.<sup>2</sup> Unfortunately, this approach has been implemented by only few centers, and because of the mostly retrospective nature of our registry, we cannot provide data on the incidence and prognostic value of LVOTO. As outlined by Dalzell, the administration of inotropes potentially increases the pressure gradient during LVOTO, which also holds true for intra-aortic counterpulsation. Although prospective data on short-term management of takotsubo cardiomyopathy are lacking, active left ventricular unloading by microaxial pumps<sup>3</sup> appears to be attractive to support left ventricular dysfunction and to reduce the pressure gradient at the same time in such patients.

Redfors and Omerovic emphasize the risk of catecholamines for treating takotsubo cardiomyopathy. In a multivariate analysis in our cohort, the use of catecholamines was a strong and independent predictor of in-hospital death (Fig. 1A). The risk of death associated with catecholamines was very high but did not differ according to sex (Fig. 1B and 1C), which suggests that other factors are responsible for the observed difference in mortality between men and women. Our retrospective analysis may have been influenced by selection bias and other factors. However, we agree that catecholamines of any nature should be administered with great caution, not only because of their potential role in the pathogenesis of takotsubo cardiomyopathy but also because of the risk of hemodynamic worsening (e.g., by the precipitation of LVOTO).



Pieroni and Bolognese emphasize the need for ruling out myocarditis in the diagnosis of takotsubo cardiomyopathy. Indeed, since MRI was not broadly available at the beginning of our study, it was not possible to use MRI data in a meaningful fashion. Patients with focal takot-

subo cardiomyopathy in our study shared most features with other patients with this condition (e.g., age, sex, and triggers), making myocarditis unlikely. However, we agree that differentiation between focal takotsubo cardiomyopathy and myocarditis is challenging. Cardiac MRI is suf-

ficient to distinguish the acute coronary syndrome, takotsubo cardiomyopathy, and myocarditis in most cases and adds valuable information, such as the presence of right ventricular involvement and intraventricular thrombi.<sup>4</sup> Thus, in addition to current diagnostic criteria, we recommend the use of cardiac MRI in patients with suspected takotsubo cardiomyopathy.

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Since publication of their article, the authors report no further potential conflict of interest.

1. De Backer O, Debonnaire P, Gevaert S, Missault L, Gheeraert P, Muyldermans L. Prevalence, associated factors and management implications of left ventricular outflow tract obstruction in takotsubo cardiomyopathy: a two-year, two-center experience. *BMC Cardiovasc Disord* 2014;14:147.
2. Citro R, Lyon AR, Meimoun P, et al. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: clinical and prognostic implications. *J Am Soc Echocardiogr* 2015;28:57-74.
3. Rashed A, Won S, Saad M, Schreiber T. Use of the Impella 2.5 left ventricular assist device in a patient with cardiogenic shock secondary to takotsubo cardiomyopathy. *BMJ Case Rep* 2015;2015..
4. Athanasiadis A, Schneider B, Sechtem U. Role of cardiovascular magnetic resonance in takotsubo cardiomyopathy. *Heart Fail Clin* 2013;9:167-76, viii.

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## Acute Methotrexate-Induced Crystal Nephropathy

**TO THE EDITOR:** Acute renal failure occurs in approximately 2% of patients who receive high-dose methotrexate for the treatment of a hematologic cancer.<sup>1-3</sup> Despite the frequency of acute renal failure and the occurrence of distinct urinary crystals in this context,<sup>4,5</sup> the presence of these crystals in human tissues has not been clearly documented. Here, we describe crystals within the kidney tubules of a patient with methotrexate-induced nephropathy.

A 52-year-old man with an aggressive B-cell lymphoma was prescribed intravenous methotrexate (1.20 g per square meter of body-surface area over a 1-hour period, followed by 0.24 g per square meter over a 23-hour period) on day 10 of a regimen of CODOX-M (dexamethasone, cyclophosphamide, doxorubicin, vincristine, rituximab, cytarabine, methotrexate, and leucovorin). The creatinine concentration in serum was below 50  $\mu\text{mol}$  per liter (0.57 mg per deciliter) before the infusion, but it increased to 116  $\mu\text{mol}$  per liter (1.31 mg per deciliter) approximately 20 hours after the infusion and reached 465  $\mu\text{mol}$  per liter (5.26 mg per deciliter) 4 days later (Fig. 1A). A small number of methotrexate-like crystals were also observed in the patient's urine (Fig. 1B and 1C) in the absence of risk factors for drug-induced precipitation or other causes of crystal nephropathy.

Examination of a renal-biopsy specimen obtained 7 days after the infusion revealed severe acute tubular injury with numerous intratubular and interstitial deposits of unique appearance (Fig. 1D–1J). These deposits were made up of compact or needle-shaped golden crystals arranged in annular structures (Fig. 1D and 1E); they were positive on methenamine silver staining (Fig. 1H) and displayed blue or gold birefringence under polarized light (Fig. 1F and 1G). Von Kossa and alizarin red stains were negative, the glomeruli appeared normal, and scarring was minimal (not shown).

Our findings indicate that intratubular crystal formation does occur in humans during the course of methotrexate-induced acute renal failure (this has previously been suspected in non-human primates; see the Supplementary Appendix, available with the full text of this letter at NEJM.org) and document the morphologic features of methotrexate-induced crystal nephropathy. In this regard, certain types of urinary crystals are known to form or to undergo structural modifications in the bladder or after micriturition because of changes in pH, temperature, or bacterial activity.

This case also shows that acute renal failure can occur even in the absence of toxic methotrexate levels in plasma 24 to 48 hours after infusion (Fig. 1A). For this reason, and because